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Synthesis of 3"-Dehydro-4-*O*-methylbarminomycin II Having an Eight-membered Acetal-azomethine Ring

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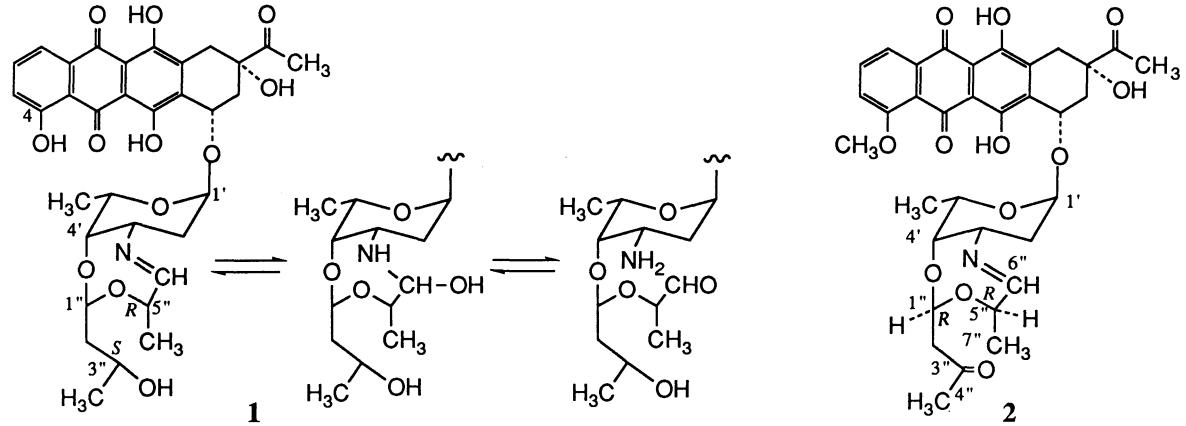
Barminomycin I and II, an extremely potent antitumor anthracyclines, have a unique eight-membered azomethine or carbinolamine structure. (1"*R*, 5"*R*)-3"-Dehydro-4-*O*-methylbarminomycin II was first synthesized through the hypothetical biogenetic intermediate.

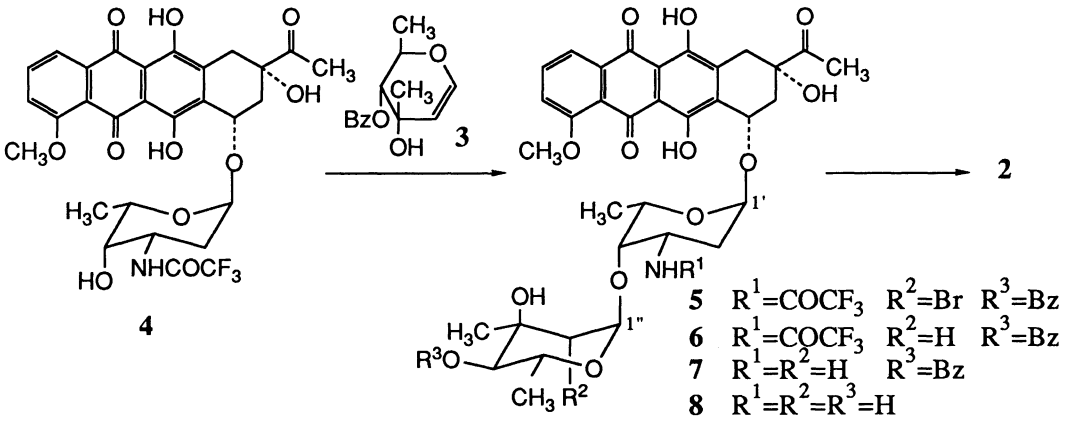
Barminomycins I and II[1,2] (**1**), are new type of anthracycline antibiotics having 4'-*O*-substituent with acetal and aldehyde functions and show the equilibrium involving the eight-membered azomethine and carbinolamine. The stereochemistries at C-3" and C-5" of **1** were determined, but C-1" position was not yet. Takahashi,[3] however, described that C-1" position of baumycins B_1 and B_2 having a similar 4'-*O*-substituent was *R*-configuration by X-ray crystallographic analysis. The cytotoxicity of barminomycins against P388 leukemia



1 **2**

cells is more than 500 times stronger than that of doxorubicin (adriamycin). Because of their activity and unique eight-membered structure, the synthesis of the analogue of **1**, (1"*R*, 5"*R*)-3"-dehydro-4-*O*-methylbarminomycin II (**2**) has been attempted starting from daunorubicin (daunomycin). The interesting 4'-*O*-side chain was presumed to be produced from 4'-*O*-glycoside (**8**) by the biologically oxidative cleavage of vicinal diol. Based on this hypothetical biogenesis, the synthetic way for **2** was designed.

Glycal (**3**) was prepared from methyl 4-*O*-benzoyl-2,6-dideoxy-3-*C*-methyl-α-D-*ribo*-hexopyranoside[4] according to Tatsuta's method.[5] Stereoselective glycosidation of *N*-trifluoroacetyldaunomycin (**4**) with **3** (NBS/CH_3CN,[6] 0 °C, 4 h, 62%) gave 4'-*O*-(4-*O*-benzoyl-2-bromo-2,6-dideoxy-3-*C*-methyl-α-D-altro-pyranosyl)-3'-*N*-trifluoroacetyldaunomycin (**5**) and no β-anomer, along with a trace of 9-*O*-glycoside. In ^1H NMR spectrum of **5**, an anomeric proton of C-1" position appeared at δ 5.02 as a doublet with J=3 Hz.[7] It showed the α-linkage at C-1". Debromination of **5** with *n*-Bu_3SnH (AIBN/benzene, 60 °C, 28 h, 49%) gave **6**. The practical removal of 3'-*N*-trifluoroacetyl group in anthracyclines having 4'-*O*-substituent has not been known



yet. Usual deprotection of trifluoroacetyl group under alkaline condition always gave the complicated products. This problem was overcome by the treatment of **6** with sodium hydroxide *in two layers* (saturated aq NaCl contained 1mol dm^{-3} NaOH/$CHCl_3$ with vigorous stirring, room temp, 2 h) to give **7** in quantitative yield, which was hydrolyzed (10% aq K_2CO_3/MeOH, 0 °C, 18 h, 30%) to afford **8**,[8] the important precursor for **2**. Finally, periodate oxidation of **8** ($NaIO_4$/MeOH-H_2O, room temp, 24 h) provided **2** as the equilibrium mixture. The addition of 10% acetic acid to the reaction mixture, followed by extraction with $CHCl_3$ gave cyclized imine **2**[9] in 10% yield. Thus, we have devised the synthesis of **2** starting from glycal **3** and *N*-trifluoroacetyldaunomycin (**4**) through the hypothetical biogenetic intermediate **8**.

References

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7) **5**: Mp 128-136 °C (decomp); $[\alpha]_D$ +82°; FABMS *m/z* 949 and 951 (M^+); ^1H NMR ($CDCl_3$) δ 1.30 (3H,*d*, *J*=6.5 Hz, 6"-*H*), 1.36 (3H, *d*, *J*=6.5 Hz, 6'-*H*), 1.46 (3H, *s*, 3"a-*H*), 3.84 (1H, br *s*, 4'-*H*), 4.05 (3H, *s*, OC*H*3), 4.20 (1H, *d*, *J*=3 Hz, 2"-*H*), 4.34 (1H, *m*, 3'-*H*), 4.45 (1H, *dq*, *J*=9.5 and 6.5 Hz, 5"-*H*), 5.02 (1H, *d*, *J*=3 Hz, 1"-*H*), 5.31 (1H, *d*, *J*=9.5 Hz, 4"-*H*), and 5.55 (1H, br *d*, *J*=3.5 Hz, 1'-*H*).

8) **8**: Mp 199-200°C (decomp); $[\alpha]_D$ +220°; FABMS *m/z* 672 (MH^+); ^1H NMR (CD_3OD) δ 1.26 (3H, *s*, 3"a-*H*), 1.27 (3H, *d*, *J*=6 Hz, 6"-*H*), 1.36 (3H, *d*, *J*=6.5 Hz, 6'-*H*), 1.77 (1H, *dd*, *J*=15 and 4 Hz, 2"-*H*), 1.86 (1H, br *dd*, *J*= 12.5 and 4 Hz, 2'-H_{eq}), 2.02 (1H, *dt*, *J*=12.5 and 3.5 Hz, 2'-H_{ax}), 2.09 (1H, br *d*, *J*=15 Hz, 2"-*H*), 3.03 (1H, *d*, *J*=9.5 Hz, 4"-*H*), 3.62 (1H, *m*, 3'-*H*), 3.64 (1H, br *s*, 4'-*H*), 4.15 (1H, m, 5"-*H*), 4.30 (1H, br *q*, *J*=6.5 Hz, 5'-*H*), 4.8 (behind HOD signal,1"-*H*), 5.47 (1H, br *d*, *J*=3.5 Hz, 1'-*H*).

9) **2**: FABMS: *m/z* 652 (MH^+), ^1H NMR (DMSO-d_6) δ 1.16 (3H, *d*, *J*=6.5 Hz, 6'-*H*), 1.29 (3H, *d*, *J*=7.0 Hz, 7"-*H*), 1.57 (1H, br *t*, 2'-H_{ax}), 1.71 (1H, br *d*, 2'-H_{eq}), 2.13 (2H, br *d*, *J*=4.5 Hz, 8-*H*), 2.25 (3H, *s*, 14-*H*), 2.43 (3H, *s*, 4"-*H*), 2.95 (2H, *ABq*, *J*=18 Hz, 10-*H*), 3.72 (1H, br *s*, 4'-*H*), 3.99 (3H, *s*, OC*H*3), 4.26 (1H, *q*, *J*=6.5 Hz, 5'-*H*), 4.94 (1H, *t*, *J*=4.5 Hz, 7-*H*), 5.2 (1H, *m*, 5"-*H*), 5.23 (1H, br *s*, 1'-*H*), 5.93 (1H, br *d*, 1"-*H*), 7.55 (1H, br *s*, 6"-*H*), 7.67 (1H, *m*, 3-*H*), and 7.93 (2H, *m*, 1 and 2-*H*).

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